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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,908	01/08/2009	Xiangbin Wang	11774-006-999	3643

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EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/594,908	**Applicant(s)** WANG ET AL.
	Examiner MARK HALVORSON	**Art Unit** 1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 December 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *27,31-33 and 41-43*.
   Claim(s) withdrawn from consideration: *34-40*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1642

Continuation of 11. does NOT place the application in condition for allowance because: The objections to the claims are withdrawn in view of Applicants new submission of claims in which the withdrawn claims are written out.

The rejections of claims 27, 31and 33 under 35 U.S.C. 112, first paragraph are withdrawn in view of Applicants amendments to claim 27.

The rejections of claims 27 and 31-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of Applicants amendments to claim 27.

The rejection of claims 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916) are withdrawn in view of Applicants amendments to claims 27, 31 and 33.

The rejections of claims 27, 31-33 and new claims 41-43 under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916, cited previously) in further view of Koga et al (Hybridoma, 1990, 9:43-56) and Robinson et al. (US Patent No. 5,618,920, issued April 8, 1997) are maintained.

In response to Applicants arguments the tri-specific antibodies disclosed in Song et al. either form circular antibodies by intramolecular disulfide bonds and are thus not linear or form polymeric antibodies by intermolecular disulfide bonds that are not single-chain antibodies, Song et al does not disclose fragments of Fc hinges at both ends of the constructs of vectors pTRI and psTRI to form a circular fragment as disclosed in WO 02/83738. Song et al does not disclose the use of fragments of Fc hinges nor that the encoded trispecific antibody would circularize after expression. Furthermore, even if the trispecific antibody of Song et al did have fragments of Fc hinges at both ends of the construct, the expressed trispecific antibody would be linear until conditions were suitable for cyclization via intermolecular dilsulfide bonds to occur. In addition, Holliger et al disclose antibody constructs that do not comprise the Fc hinge fragments and would not form a circular fragment as disclosed in WO 02/83738 under suitable conditions such as when used in vivo.

Applicants argue that it is undeniable that neither Song et al. nor Holliger et al.
disclose an anti-CEA antigen binding fragment comprising SEQ 1D NO:1. Applicants further argue that while the Office Action quotes Robinson et al. as stating "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity," there is no guarantee that Robinson et al.'s would have definitely uncovered at the desired sequences.
Applicants arguments have been considered but are not persuasive. The court has found that a compound may be found anticipated, or held obvious, when the prior art was unaware of the sequence a molecule had, or would have if made. In re Crish, 393 F.3d 125 (Fed Cir 2004) (affirming anticipation where nucleic acid was described by prior art but its sequence was not revealed by prior art); In re Kubin, 561 F.3d 1351 (Fed Cir 2009) (affirming obviousness where nucleic acid described by sequence and other features had not been made earlier). The anti-CEA monoclonal antibody used in the present invention was described date by Koga et al prior to Applicants filing and Applicants have not demonstrated that the anti-CEA monoclonal antibody described by Koga et al was not publically available prior to the effective filing date of the present invention. One of ordinary skill in the art would have had a reasonable expectation of success in making scFv using Koga et al' s monoclonal antibody to CEA because Robinson et al teach the determination of nucleic acids encoding VH and VL of any known antibody.

In response to Applicants arguments that there was not sufficient direction and nor guidance in Robinson et al. and undue experimentation would have been needed to make the invention claimed in amended Claim 27 and dependent claims 31-33 and 41-43, prior art is presumed to be operable/enabling MPEP 2121. Furthermore, MPEP 2121, part III states
A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." Impax Labs. Inc. v. Aventis Pharm . Inc., 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006). See also MPEP § 2122.

Applicant is reminded that when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Thus, Applicants' argument that the tri-specific antibody comprising SEQ ID NO:1 of Song e al in view of Holliger et al, Koga et al and Robinson et al is nonenabling (e.g., inoperable) are not found persuasive in the absence of objective evidence..